EUROTHERM

CONTROLS
PROCESS AUTOMATION
RECORDERS

Pharmaceutical/Biotechnology Validation of the 5000 Series Recorder

Applies to V1.3 of the 5000 series product software

Introduction

Pharmaceutical and biotechnology manufacturing sites throughout the world are very concerned about quality, data traceability, instrument accuracy and stability. This is driven by ever increasing professionalism and the requirements of the US Food and Drugs Administration (FDA).

These sites manufacture drugs for human and animal use, pre-packed sterile equipment such as sutures, syringes etc. and primarily in the USA, food products. Product cannot be imported or sold into the USA market place unless it is produced in accordance with the FDA requirements.

The USA Food and Drugs Administration (FDA) validate a production process only. The equipment used on the validated process is not itself, validated. It is therefore not possible for an instrument manufacturer to claim that an instrument, to be used on a process, has been 'FDA approved'.

It is the responsibility of the company requesting FDA approval to satisfy themselves and the FDA inspectors that the manufacturing process is of satisfactory quality with full traceability.

Summary

Do the FDA accept Electronic Records?
Yes, see FDA document 21 CFR Part 11 at http://www.fda.gov/ora/compliance_ref/part11/

What are the details of the Eurotherm ISO9000 Certificate?
The Eurotherm Limited ISO9001 certificate, including TickIT, is issued by Lloyd's Register Quality Assurance Limited, certificate number LRQ0871739. First issued April 1990 with TickIT added in 1994.

International Company with manufacturing base back to 1966

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Registered Office Carlisle Place London SW1P 1BX Registered in England No 853008

This shows a history of high quality production and design.

Products and software designed and manufactured in an ISO9000/TickIT environment
This shows that Eurotherm are currently working within respected design/manufacturing procedures that are referred directly to in the GAMP specifications.

Standard industrial, volume shipped, product with no special changes for FDA
If the product has any design problems, other customers will have found them before the pharmaceutical companies!

Logged data is in binary format, encoded and checksummed to inhibit data tampering
Stops accidental and malicious modification to the archived data.

Data can be archived to local disk and/or via comms. to secure optical WORM drive on PC running Review or third party software
Once in the PC environment, the data can be stored and normal computer librarianship, security and backups can take place.

Company would welcome inspection from pharmaceutical inspectors
Eurotherm will welcome any inspection of its manufacturing facilities and development site. Inspections have been successfully completed over many years, by several major pharmaceutical companies.

Company history

Eurotherm was established in 1965, recognising the new opportunities that were emerging for transistor components and the emerging requirements for long-term data recording. Since then we have diversified, leading from the front with an unmatched vision in product design and application engineering. Now with three decades of experience in process measurement behind us, no one has a greater understanding of real-world problems and no one is placed better to provide creative practical solutions to the worlds most demanding application challenges.

Eurotherm Company Management systems

To help the pharmaceutical and biotechnology manufacturing companies satisfy themselves that Eurotherm equipment is suitable for their process, all design of Eurotherm product and software is carried out in an ISO9001 environment incorporating TickIT software management systems. "*This approach supports and interprets the ISO 9000-3 guidelines for software, and its associated 'TickIT' certification scheme, by providing suppliers with practical tools and methods to implement an appropriate quality management system within their organisation. In the future, it is anticipated that GAMP Forum will further develop its Guidelines for Suppliers to converge with the software industry's quality schemes – notably 'TickIT' – supported by an Industry-sector document as appropriate*." – GAMP Guide Validation of Automated Systems in Pharmaceutical Manufacture Version: V3.0, March 1998.

The TickIT scheme has been developed by a team of leading quality management specialists drawn from the British standards committee, BRD/3/1, the UK Software industry and interested European Organisations such as KEMA, Qualience, and SWEDAC.

Companies certificated to ISO9001 under TickIT are in over 40 different Countries world-wide, these include every country in the European Union, USA, Canada, Mexico, Brazil, Australia and many countries in Asia, including China, India, Japan, South Korea, and Taiwan.

CERTIFICATE OF APPROVAL

This is to certify that the Quality Management System of:

Eurotherm Limited
Worthing, West Sussex
United Kingdom

has been approved by Lloyd's Register Quality Assurance to the following Quality Management System Standards:

ISO 9001: 1994
The TickIT Guide Issue 4

The Quality Management System is applicable to:

Design, manufacture, service and calibration of process control, monitoring and recording equipment, including development of related software in accordance with TickIT.
Design, management of manufacture and service of process control systems, including development of application software in accordance with TickIT.
Stockholding of circular chart recorders, interface modules, spares and consumables.

Approval Certificate No: LRQ 0871726

Original Approval: 27 April 1990
Current Certificate: 7 November 2000
Certificate Expiry: 31 March 2003

on behalf of LRQA Coventry

LLOYD'S REGISTER QUALITY ASSURANCE

5000 product features

Overview

The 5000 Series acts as the interface between the process plant and operators. It acquires and displays process data from sensors on the process using input boards fitted internally, this data is then stored in a binary file format within the products internal flash memory (non-volatile). This data is not accessible and therefore cannot be tampered with or deleted, these data files are then copied automatically to archive media or over Ethernet to a file server. Once the internal instrument memory is full it is overwritten on a first in, first out basis.

Inputs

The inputs to the instrument are all non-multiplexed, solid state circuits updating the PV (and alarms) of the instrument 8 times per second. Each input signal has its own circuit, isolated from every other input signal and ground to 250Vac. Each input can be individually configured for all common process signals such as thermocouple, RTD, V, Mv, mA, resistance and contact input.

Data Archiving

Process values are initially logged, at the configured time interval, with full time/date information to data files within the 5000 Series products non-volatile flash memory. The values logged are a single snapshot of the PV at the time of the log, these data files are unique within the instrument, are stored in a packed binary format, each time-stamped record having a checksum to ensure integrity, whilst within the instrument there is no write access to this data from external sources. To help ensure that the minimum of data is lost in the very unusual case where flash memory may fail no data file greater than 400kbyte is generated.

Display

Data is viewed on a 12.1 inch SVGA TFT LCD screen 800*600 resolution (5180V) or a 5.5 inch ¼ VGA TFT LCD 320*240 resolution (5100V). The display assembly has a toughened touch panel with a polyester coating that is impervious to virtually any chemical attack.
Process data can be displayed in a variety of standard display types or the optional Screen Builder can be used to generate displays types as specified by the user.

21 CFR Part 11 - Electronic Records & Electronic Signatures

Security is a very important consideration in data acquisition projects and is a standard feature on all 5000 Series recorders.

The final ruling 21 CFR Part11 (20 March 1997) defines the 5000 Series recorder as a 'closed system' in being*…"(4) Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system."* … *(21 CFR Part11, Subpart A section 11.3 (4)).* The 5000 Series features aid production process validation in the following ways:

21 CFR Part11, Subpart B Section 11.10 ***Controls for closed systems****.*

21 CFR Part11, Subpart B section 11.10 (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.
The configuration of the recorder can be carried out either online- or off-line, where a password MUST first be entered to gain access. Once configured, the binary and checksummed, instrument configuration file can be held securely for any validation and back-up requirements. Process data is stored automatically within the parameters laid out in the configuration, these data files are in a binary format with a checksums to confirm against any attempted modification. This file format detail is NOT published by Eurotherm Limited.

21 CFR Part11, Subpart B section 11.10 (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.
The raw process data files from the recorder can be copied to the local archive media (floppy disk or PC card) or using the FTP option directly to a server on a local area network, using the integral 10BaseT Ethernet connection over TCP/IP. The raw data files are designed to be imported into Eurotherm Review software to enable post analysis of the data and generation of paper records if required.

21 CFR Part11, Subpart B section 11.10 (c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.
Data should either be printed onto paper records for storage or should be reliably and securely copied before existing file storage technology becomes obsolete and difficult to support. This is a procedural process and outside the scope of Eurotherm Limited.

21 CFR Part11, Subpart B section 11.10 (d) Limiting system access to authorised individuals.
Access can be easily limited to authorised individuals using the standard user name/password feature within the Series 5000 recorder. This gives specific access permissions to specific individuals with their own user name/password.

21 CFR Part11, Subpart B section 11.10 (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.
When using the optional batch functionality of the 5000 Series recorder, any operation to start/stop the process is recorded within the binary data file generated at the time, this information includes date/time and the user name of the operator that has performed the operation.

21 CFR Part11, Subpart B section 11.10 (f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
The configuration parameters of the 5000 Series can force particular operational interlocks with the use of relay contacts and the associated overall process design. The use of these interlocks need to be as part of the overall design of the process and can not be limited only to the 5000 instrument.

21 CFR Part11, Subpart B section 11.10 (g) Use of authority checks to ensure that only authorised individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
When used with the optional batch functionality, the 5000 Series recorder will log the user name of any operator that starts or stops a process batch along with other batch parameters. The authority checks and password delinquency are outside the scope of Eurotherm Limited.

21 CFR Part11, Subpart B section 11.10 (h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
This is outside the scope of Eurotherm Ltd. and procedural where checks are periodically carried out to ensure that the instrument configuration is identical to that archived at system acceptance. Regular calibration checks should also be included to ensure that full system data can be relied upon.

21 CFR Part11, Subpart B section 11.10 (i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

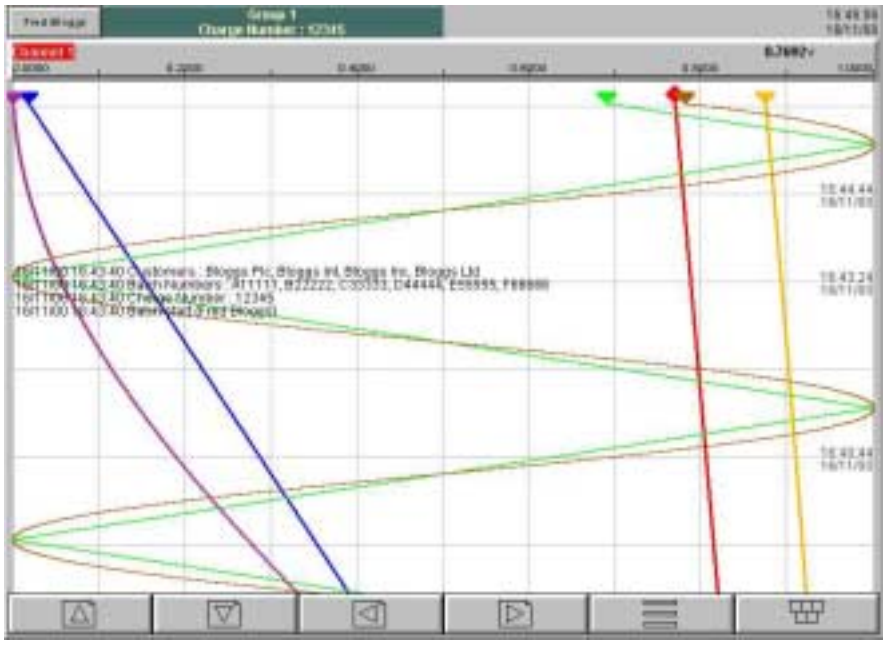
This is generally outside the scope of Eurotherm Limited. Training should be carried out as part of system acceptance and the use of a fully documented operations manual is important. The 5000 Series recorder ensures that only those personnel who have appropriate access levels are able to perform certain tasks. It is important that personnel access levels and training are kept up to date and passwords changed regularly to maintain security. Product training can be organised by your local Eurotherm representative at any time.

21 CFR Part11, Subpart B section 11.10 (j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.
This is outside the scope of Eurotherm Limited. The 5000 Series recorder aids this by identifying in the batch record, the operator responsible for starting/stopping any batch.

21 CFR Part11, Subpart B section 11.10(k) Use of appropriate controls over systems documentation including:
(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.
This is the responsibility of the process management in association with organisations employed to carry out any required works and is outside the scope of Eurotherm Limited.

Batch

The 5000 Series batch recorder offers unparalleled features in logging process data for batch type applications. Up to six configurable fields can be enabled to hold information such as ‘batch number’, ‘charge number’, ‘supervisor name’, ‘product code’ etc. The batch record is unable to start until the process operator has logged in, using his unique login and password and completed ALL required data fields. Once started, the operator’s user name is logged with the batch and process data. At the end of a batch, the operator has to again login and full details are again recorded. If the process is a continuous one, the 5000 instrument may be configured to record data associated only with batch starts. This batch data can then be archived and reported upon on a batch by batch basis using Eurotherm Review software.



Communications

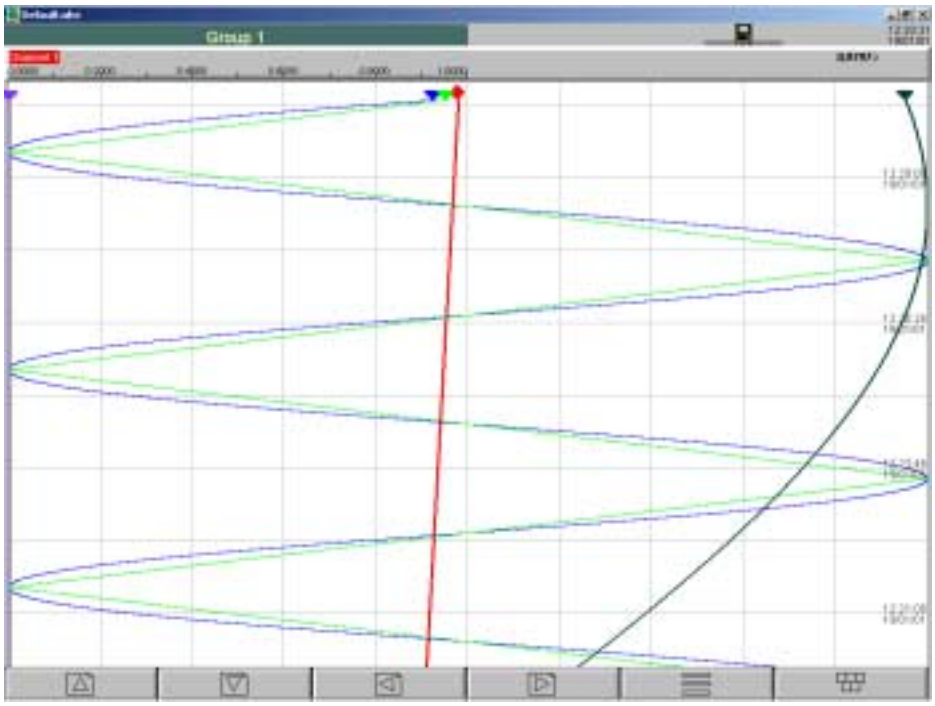
Communications facilities are becoming an increasingly important asset in modern production instrumentation and control. The 5000 Series comes as standard with an RJ45 10BaseT Ethernet connection. This connection can be securely accessed for the following functions as detailed below: FTP File transfer, Bridge 5000 remote viewer and connection to Review software. Future releases of software will support the Modbus TCP protocol over Ethernet.

FTP

The 5000 Series recorder can be configured to act as an FTP Server and/or and FTP Client, this means that the instrument can automatically send data files to a server on the network or an application running on a PC can request data files from the instrument (or both!). All of this under individual username/password control.

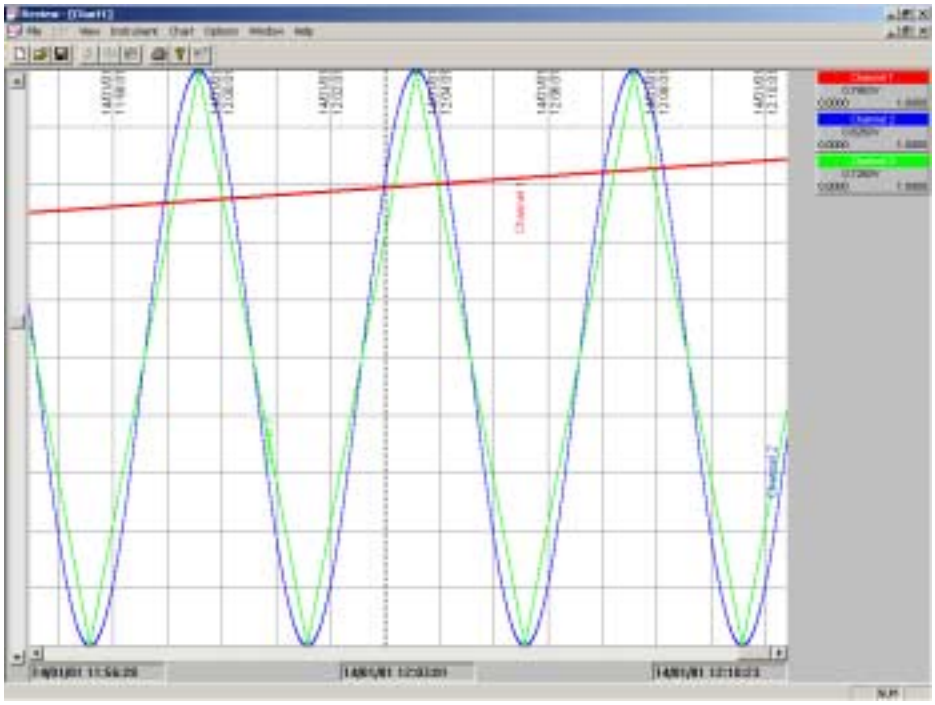
Remote viewing (bridge 5000)

Bridge 5000 software enables the 5000 instrument to be viewed from any PC connected to the network that the instrument is on. This viewing is under username/password control. It does not interact in any way with the process running on the instrument, but merely views the process as if you were stood next to the instrument display. It is a convenient way for an on-call engineer to view a process from home before being called out or for a supervisor to check progress from their desk.



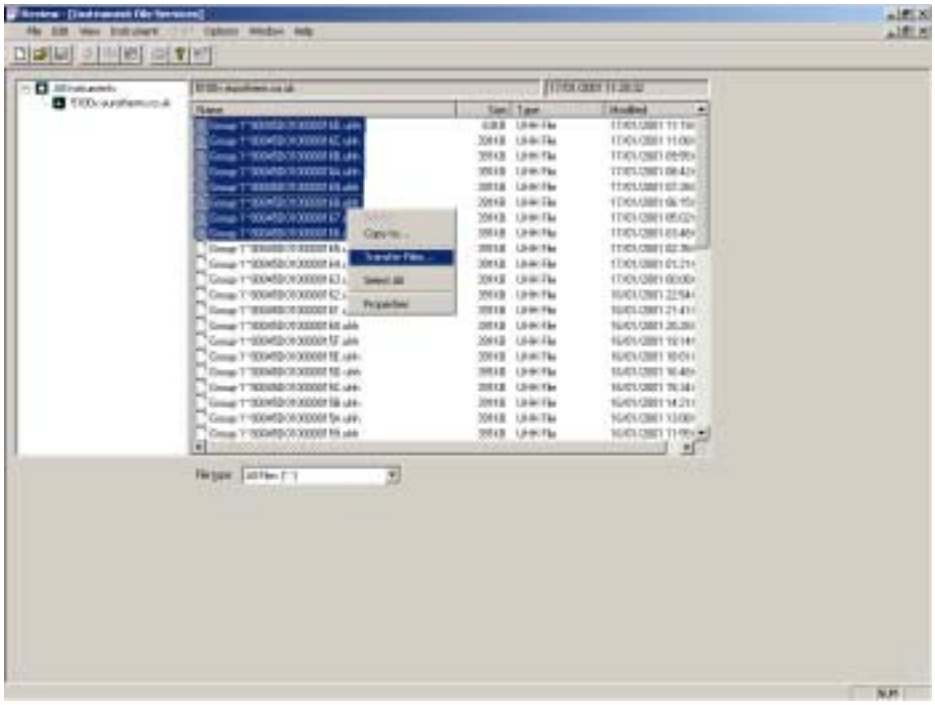
Post process Data Analysis (review)

Eurotherm's Review software combines a database that takes a copy of process data from any of Eurotherm's recorder range to create a single database covering multiple instruments. This data can then be reported on in several formats to create displayed or printed charts of the original data. This can also be exported in ASCII format for further analysis as required.



Transfer of Data

Data is transferred from the raw data files in the instrument into the Review database in a 3 pass system, where the raw data file is first checked to ensure that there is no corruption, the data is then transferred across into the Review database (without affecting the raw data file which remains intact), then the data that has been added to the Review database is rechecked with the original raw data file to ensure that no corruption has taken place.



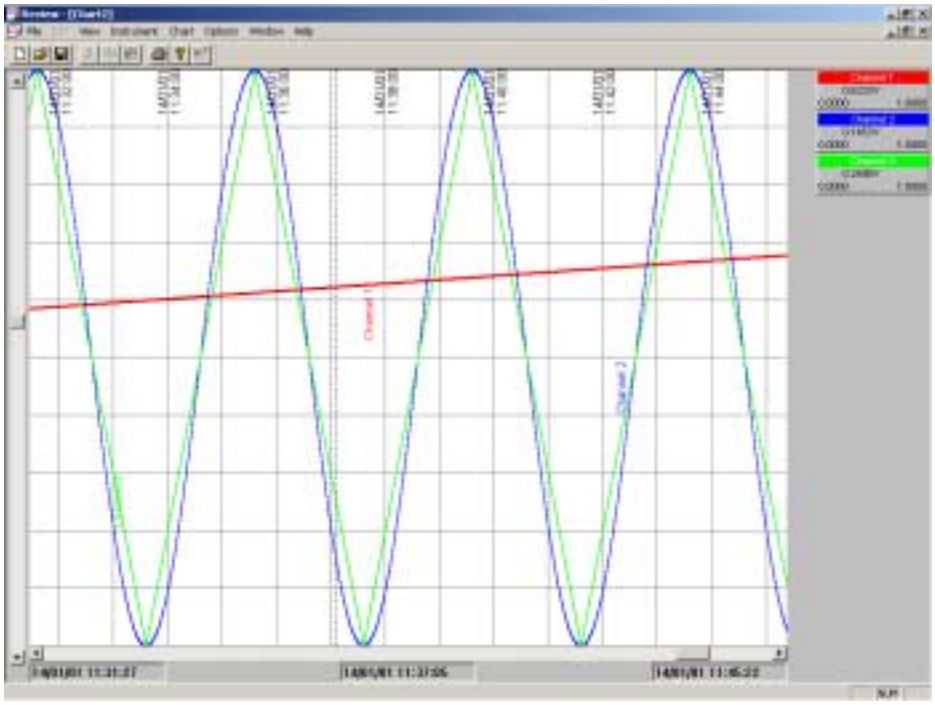
Database structures

The Review database is held as a single packed binary file that has a full checksum to ensure that the data it contains is not corrupted in any way.

Analysis

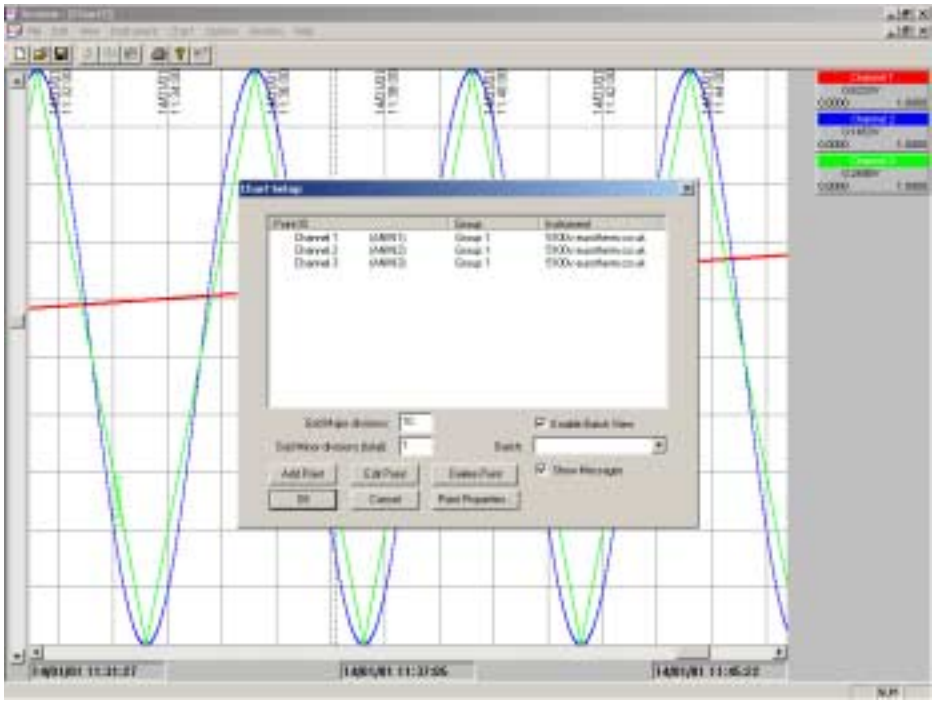
Data points from any instrument in the database can be displayed as a chart on the PC screen. This can then be exported as ASCII data for such analysis packages as Excel™, again the data in the Review database remains untouched. The chart display includes features such as:

- Review continuous or batch data
- Clear chart time base
- Time base compression to get more time on the screen
- Cursor bar with associated digital values for all channels at a particular time
- The same trace colours as on the instrument
- All traces annotated with channel tag



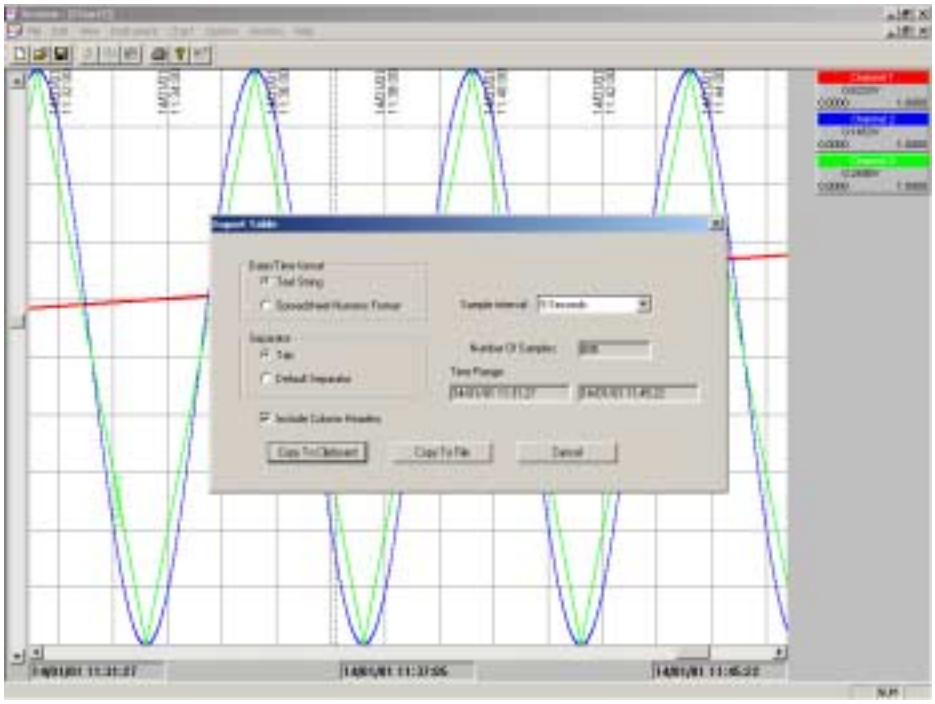
Batch Analysis

Data from a specific batch can be selected and displayed, printed or exported as an ASCII data file. Again the Review database is not written to in any of this process.



Export of Data

Process data can be exported in an ASCII format for any data points defined and viewed in a chart on the PC screen. Once in the ASCII format however the data becomes unsecure, however is can be reproduced again from the more secure Review database.



Further information

http://www.fda.gov - FDA Home page
http://www.fda.gov/opacom/hpview.html - The Food and Drug Administration: An Overview
http://www.ispe.org/gampinto.htm - Where to order **G**ood **A**utomated **M**anufacturing **P**ractice
http://www.fda.gov/cder/esig/index.htm - Document that proves FDA acceptance of electronic data
http://www.21cfr11.com/ - Website concerned only with 21CFR part 11
http://www.fda.gov/ora/compliance_ref/part11/FRs/background/pt11finr.pdf - 21CFR11 Final rule

-The Good Laboratory Practice Regulations 1997	ISBN 0 11 064105 1
-Quality Systems for Sterile Medical Devices and Surgical Products 1990: Good Manufacturing Practice	ISBN 0 11 321341 7
-Rules and Guidance for Pharmaceutical Manufacturers 1997: Incorporating - EC Guide to Good Manufacturing Practice [GMP] and Good Distribution Practice	ISBN 0 11 321995 4
-Guidelines for Good Manufacturing Practice of Cosmetic Products (GMPC)	ISBN 9 28 712849 9
-Good Manufacturing Practices for Pharmaceuticals	ISBN 0 82 479770 1
-The Rules Governing Medicinal Products in the European Union Vol4: Pharmaceutical Legislation: Good Manufacturing Practices: Medicinal Products for Human and Veterinary Use	9 28 282029 7

Any reference to 21 CFR Part 11 refers to the Food and Drug Administration federal register document 21 CFR Part 11 Electronic Records; Electronic Signatures; Final Rule dated 20 March 1997 [Docket No. 92N-0251]

All references valid January 2001